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The Neuromuscular Blocking Effects and Pharmacokinetics of ORG 9426 and ORG 9616 in the Cat

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The neuromuscular blocking effects and pharmacokinetics of ORG 9426, 1.5 mg/kg and ORG 9616, 1.2 mg/kg iv, two new nondepolarizing neuromuscular blocking drugs, were studied in 28 cats (*i.e.*, 14 cats with each drug) with and without renal pedicle ligation. A gas chromatographic assay was used to determine the concentrations of ORG 9426 and ORG 9616 and its desacetyl metabolites in plasma, urine, bile, and liver. The duration of neuromuscular blockade of both drugs was not altered by ligation of renal pedicles. Plasma clearance of ORG 9426 was slower in cats with ligated renal pedicles ($P < 0.01$). With ORG 9616, mean elimination half-life was slower and mean residence time longer in cats with renal pedicle ligation. Otherwise, there was no significant differences with any pharmacokinetic variables in cats with and without renal pedicle ligation. Only 8.7 ± 5.7% (SD) and 6.0 ± 2.8% of an injected dose of ORG 9426 and ORG 9616 was excreted into the urine, respectively. Conversely, 54.4 ± 9.2% and 52.4 ± 9.2% of an injected dose of ORG 9426 and 35.7 ± 12.2% and 46.8 ± 9.7% of ORG 9616 were excreted into the bile in cats without and with renal pedicle ligation, respectively. Finally, 21.3 ± 6.5% and 33.5 ± 15.6% of ORG 9426 and 14.0 ± 3.2% and 18.1 ± 5.6% of ORG 9616 were in the liver 6 h after injection in cats without and with renal pedicle ligation respectively. The authors were able to account for the biodisposition of 84.4% and 85.9% of an injected dose of ORG 9426 in cats without and with renal pedicle ligation respectively. Because none of the desacetyl metabolites were detected in plasma, urine, bile, or liver, and most of the ORG 9426 was accounted for in the unchanged form, little or no metabolism apparently takes place. The authors conclude that ORG 9426 has an intermediate duration of action and is cleared from plasma primarily due to hepatic uptake and biliary excretion of the unchanged drug. In contrast, approximately 40% of the ORG 9616 recovered was in the form of its 3-desacetyl metabolite. However, the authors were able to recover only 55.7% and 64.6% of an injected dose of ORG 9616 with and without renal pedicle ligation, respectively. The authors conclude that ORG 9616 has a short duration of action and is cleared from plasma by metabolism and biliary excretion. (Key words: Neuromuscular relaxants: ORG 9426; ORG 9616. Pharmacokinetics: ORG 9426; ORG 9616.)

BECAUSE OF ITS RAPID ONSET and short duration of neuromuscular blockade, succinylcholine is commonly used to facilitate tracheal intubation. Yet, succinylcholine has many adverse effects. During the last 15 yr, much research has been directed toward designing and developing a neuromuscular blocking drug with a time course of neuromuscular blockade closely resembling that of succinylcholine but without its side effects believed to be inherent to its depolarizing action at the neuromuscular junction.

The above goal has been approached either by the development of compounds with nondepolarizing actions at the neuromuscular junction undergoing rapid enzyme hydrolysis or other type of chemical inactivation (*e.g.*, atracurium, mivacurium), or by creating compounds the neuromuscular effects of which are terminated by increased total plasma clearance secondary to rapid tissue uptake and biotransformation (*e.g.*, vecuronium). Until recently, neither of the above approaches has produced the nondepolarizing drug with the time course of action similar to that of succinylcholine.[1] However, both directions of drug design have provided greater understanding of physicochemical, pharmacokinetic, and metabolic factors governing the time course of neuromuscular blocking activity and the side effects of this class of drugs. Typical examples illustrating the above are the development of mivacurium,[2] and more recently, ORG 9426 and ORG 9616. All three compounds have recently reached the stage of clinical investigation. ORG 9616 and ORG 9426 are, in fact, the 17-butyril and the 2-morpholino 16 allyl pyrrolidine derivatives of vecuronium and 3-desacetylvecuronium, respectively (fig. 1). Pharmacologic testing[3],†† revealed both compounds to be significantly faster in onset of neuromuscular blockade than vecuronium in various animal species. In the above studies, ORG 9616, in most animal species, produced a neuromuscular blockade similar to that observed with succinylcholine in humans.[3] ORG 9426 showed approximately one-third of

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†† Booij LHDJ, Crul JG, Agoston S: Cardiovascular and neuromuscular blocking effects of two new nondepolarizing muscle relaxants in anesthetized beagle dogs and two species of monkeys. (In press).

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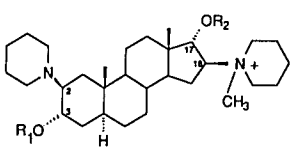
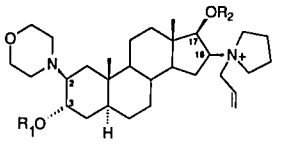
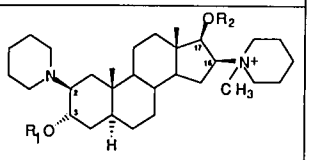
COMPOUND	R_1	R_2	STRUCTURE
ORG 9616	Acetyl	Butyryl	
ORG 9426	H	Acetyl	
Vecuronium	Acetyl	Acetyl	

FIG. 1. Structural formulas for ORG 9426, ORG 9616, and vecuronium.

the onset time of vecuronium with a slightly shorter or similar duration of action. The lack of cardiovascular side effects and its stability in aqueous solution were also important properties for selecting ORG 9426 for further clinical development.

Aiming to help understand the reason for the time-course profile observed in the pharmacologic screening of the above two drugs, and recognizing that clinical trials are beginning with both drugs, we sought to determine the pharmacokinetic disposition and biotransformation together with the neuromuscular blocking effects of ORG 9616 and ORG 9426 in anesthetized cats with and without ligated renal pedicles. Additionally, in a separate series of experiments in cats, the influence of the hepatic first-pass effect on the neuromuscular activity of both compounds were studied during hepatic exclusion and after intraportal injection.

Materials and Methods

All studies were approved by our Committee on Animal Research. Initially 28 cats of either sex 2–4 kg, were studied, 14 of which had their renal pedicles bilaterally ligated. Anesthesia was induced with pentobarbital, 40 mg/kg intraperitoneally and maintained with additional doses of 12 mg/kg as required. After tracheal intubation *via* tracheostomy, ventilation was controlled (FI_{O_2} = 0.2) *via* a Harvard respirator sufficient to maintain end-tidal P_{CO_2} between 30 and 40 mmHg. Arterial blood pressure and heart rate were monitored using a Statham pressure transducer *via* a cannula inserted into the carotid artery. Rectal temperature was maintained at 37–38° C using an infrared heating lamp. To maintain intravascular fluid balance, 2.5% glucose in 0.45% saline was infused at a rate of 8 $ml \cdot kg^{-1} \cdot h^{-1}$ through a catheter inserted into the jugular vein. The indirectly evoked twitch tension (resting tension, 200–230 g) of the anterior tibialis muscle elicited by supramaximal square-wave stimuli (applied to the peroneal nerve) of 0.2 ms duration and 0.1 Hz (S44 Grass stimulator and SIU stimulus isolation unit) was continuously quantitated by means of a force-displacement transducer and recorded. After a laparotomy was performed, the gall bladder was visualized and the cystic duct ligated. The common bile duct was cannulated for collection of bile from all 28 cats. In 14 of the cats, the urinary bladder was cannulated (through the urethea) and urine samples were subsequently collected. In the remaining 14 cats, the renal pedicles were ligated to allow determination of the pharmacokinetics of ORG 9426 or ORG 9616 in the absence of renal function.

After twitch tension, arterial blood pressure and heart rate had been stable and unchanged for 30 min blank samples of blood, urine, and bile were collected. Thereafter, the hematocrit and arterial blood gases were determined at least once an hour throughout each experiment. Only experiments showing less than 10 percent deviation from control values of the above variables were included in the final data analysis. ORG 9426, 1.5 mg/kg or ORG 9616, 1.2 mg/kg was given as an iv bolus. To provide sufficiently high plasma concentrations for a meaningful pharmacokinetic analysis, a dose times the ED_{90} (*i.e.*, that dose which causes a 90% reduction in twitch tension) of each compound was employed. Onset time (from injection of muscle relaxant to maximum depression of twitch tension), duration of action (from injection of muscle relaxant until return of twitch tension to 25% of the control value), and recovery index (from 25–75% recovery of control twitch tension) were determined. Blood samples were collected from the carotid artery 2, 5, 7, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min after administration of ORG 9426 or ORG 9616. Each time 2 ml of blood was withdrawn—a total 30 ml during a 6 h period. Blood samples were centrifuged (13,000 g) for 1 min. The plasma layer was removed and acidified to a *p*H of approximately 5 by the addition of 1 M phosphoric acid (25 μl/ml plasma). Bile and urine samples were obtained at 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min and buffered with 1 M phosphoric acid to bring the *p*H of the samples to 5.0 ± 0.2. At the end of the experiment, the liver was excised, washed with distilled water, and mixed in a blender with 1 M sodium dihydrogen phosphate to a final volume of 400 ml.

A specimen of this mixture was homogenized and with all other samples frozen at −30° C until time of analysis. At the end of the experiment, the animals were killed with pentobarbital 150 mg/kg, and atracurium 15 mg/

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kg. The concentration of ORG 9426, ORG 9616, and its desacetyl metabolites were analyzed by a gas chromatographic assay developed for pancuronium, vecuronium, pipecuronium, and their 3-desacetyl analogues.[4] For both ORG 9426 and ORG 9616, the sensitivity of the assay was 5 ng/ml and the coefficient of variation 10%. The assay showed good linearity in plasma, bile, urine, and liver over a 3–5000 ng/ml range. Multiexponential kinetic equations were fitted to the plasma concentration decay curves by means of a BMDP computer program. The kinetic model best describing the plasma decay curves was selected according to standard statistical criteria.[5]

An additional ten cats were anesthetized with sodium pentobarbital 40 mg/kg intraperitoneally. Ventilation, cardiovascular, body temperature, and neuromuscular monitoring were performed as described in the previous experimental series. In order to study the influence of the hepatic uptake on the neuromuscular activity of ORG 9426 and ORG 9616, the "liver shunt" experimental model[6] was established. This method allows the liver to be temporarily excluded from the systemic circulation by a surgical procedure that combines shunting of the blood from the portal vein to the inferior vena cava with temporary closure of the hepatic artery and the portal vein behind the shunt. The technique also allows drugs to be injected intraportally when the normal hepatic circulation is re-established. Using this model, the ED90 of ORG 9426 (0.25 mg/kg) and ORG 9616 (0.2 mg/kg) dissolved in 0.2 ml of saline was injected over 10 s on four occasions, each time 1 h after the complete recovery of twitch tension to control value from the previous injection. The first and fourth administration served as controls with the test drug injected iv under normal conditions in the hepatic blood flow. Three minutes before the second iv injection the hepatic artery and proximal portal vein were clamped and the shunt opened and the neuromuscular effects of the second dose observed. The period of hepatic exclusions lasted 10 min after which the normal hepatic blood flow was restored. The third dose was administered intraportally with a catheter inserted into the portal vein with the shunt closed.

TABLE 1. Time Course (min) of ORG 9426 (1.5 mg/kg) and ORG 9616 (1.2 mg/kg) IV in Cats with and without Renal Pedicle Ligation

Drug	Renal Pedicle	N	Onset	Duration	Recovery Index
ORG 9426	Intact	7	0.8 ± 0.7	26.4 ± 4.5	6.7 ± 2.1
ORG 9426	Ligated	7	0.9 ± 0.6	24.7 ± 8.4	7.4 ± 4.5
ORG 9616	Intact	7	0.7 ± 0.4	14.6 ± 5.7†	6.3 ± 3.7
ORG 9616	Ligated	7	0.5 ± 0.2	15.4 ± 2.3†	3.8 ± 1.4*

Mean ± SD.
* Significantly different from ORG 9616 intact ($P < 0.05$).
† Significantly different from both the ORG 9426 groups ($P < 0.05$).

TABLE 2. The Influence of Hepatic Uptake on the Neuromuscular Blockade (min) Induced by ORG 9426 (0.3 mg/kg) and ORG 9616 (0.2 mg/kg) in the Cat

Condition	Drug	Onset	Duration	Recovery Index
IV injection	ORG 9426	1.0 ± 0.3	6.8 ± 0.2	1.6 ± 0.5
	ORG 9616	1.2 ± 0.4	4.0 ± 1.3	0.9 ± 0.4
IV injection (hepatic vessels occluded)	ORG 9426	0.7 ± 0.1	19.5 ± 1.5*	3.1 ± 0.5
	ORG 9616	1.0 ± 0.2	7.3 ± 1.8	1.5 ± 0.7
Intraportal injection	ORG 9426	1.1 ± 0.3	5.3 ± 1.5	1.4 ± 0.1
	ORG 9616	1.0 ± 0.2	3.4 ± 1.0	0.9 ± 0.3
IV injection	ORG 9426	1.0 ± 0.3	7.2 ± 2.2	1.8 ± 0.6
	ORG 9616	1.0 ± 0.2	4.0 ± 1.2	0.9 ± 0.4

Mean ± SD. N = 5.
* Significantly longer than the other durations of action from ORG 9426.

STATISTICAL ANALYSIS

For comparison of the data in cats with and without ligation of renal pedicles or ORG 9616 *versus* ORG 9426, the Mann-Whitney U Test was used. In the second series of experiments, differences between onset time, duration of action, and recovery rate after the four modes of injection of each drug were tested by one-way analysis of variance. Differences were considered significant at $P < 0.05$.

Results

The time course of the large doses (*i.e.*, 6× ED_{90}) of ORG 9426 and ORG 9616 are summarized in table 1,

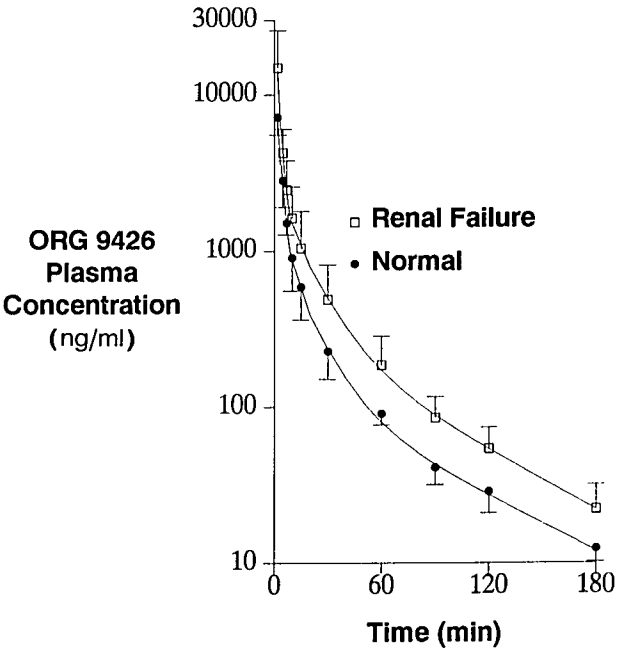

FIG. 2. Plasma decay curves for ORG 9426. Symbols represent mean ± SD. The lines are drawn to facilitate visualization of the data.

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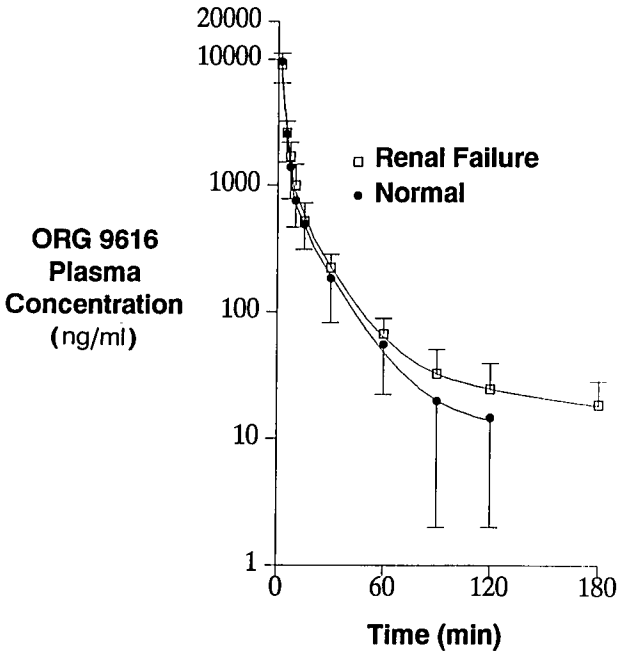

FIG. 3. Plasma decay curves for ORG 9616. Symbols represent mean ± SD. The lines are drawn to facilitate visualization of the data.

and those after the ED_{90} dose in the hepatic uptake studies are given in table 2. Renal pedicle ligation did not alter any of the time course variables of ORG 9426 but shortened significantly the recovery index of ORG 9616 ($P < 0.05$). In both the intact and renal pedicle ligated groups, the duration of action of ORG 9616 was significantly shorter ($P < 0.05$) than that of ORG 9426 (table 1). Hepatic uptake appeared to alter the time course of action of ORG 9426 only. The duration of action of ORG 9426 was significantly prolonged ($P < 0.05$) by temporary hepatic exclusion (table 2).

The plasma concentrations of ORG 9426 and ORG 9616 are displayed in figures 2 and 3, respectively. The pharmacokinetic variables of ORG 9426 and ORG 9616 in cats with and without renal pedicle ligation are summarized in table 3. Renal pedicle ligation significantly slowed the clearance and tended to decrease the volume of distribution at steady-state (Vd_{ss}) of ORG 9426; however, the differences in the Vd_{ss} were not statistically significant. Unlike ORG 9426, renal pedicle ligation significantly prolonged the elimination half-life and mean residence time of ORG 9616 that was associated with reduced clearance and slightly increased Vd_{ss}. The apparent differences in the Vd_{ss} and clearance were not statistically significant (table 3). The total recovery of ORG 9426 in the urine, bile, and liver was 86% and 84% of the injected dose in cats with and without renal pedicle ligation, respectively. More importantly, renal pedicle ligation did not alter the biliary excretion of ORG 9426 which was about 50% of the injected dose in both experimental groups within 120 min after drug administration (table 4). No desacetyl metabolites of ORG 9426 were identified in plasma, urine, bile, or liver.

In contrast to ORG 9426, the recovery of the unchanged part of ORG 9616 amounted to only 31% and 29% of the injected dose in animals with and without renal pedicle ligation, respectively (tables 5–7). This compound undergoes substantial biotransformation to its 3-desacetyl (3-OH) metabolite. The recovery of the 3-desacetyl compound was 1.5%, 15.3%, and 9.8% of the injected dose in the urine, bile, and liver in the intact animals. Renal pedicle ligation slightly increased the formation of the 3-OH metabolite to 19% and 14% of the injected dose in the bile and the liver, respectively (tables 5–7). The total recovery of the parent compound together with the 3-desacetyl metabolite was 55% and 65% of the injected dose of ORG 9616 within 8 h in animals with and without renal pedicle ligation, respectively. Specifically, 4.2% and 21.3% of the injected dose of ORG 9616 and ORG 9426 could be recovered from the liver as unchanged form in the intact animals at the end of the observation period. The corresponding values in cats with ligated renal pedicles were 3.6% and 33.5% of the injected dose of ORG 9616 and ORG 9426, respectively (tables 4 and 7).

TABLE 3. Pharmacokinetic Variables of ORG 9426 (1.5 mg/kg) and ORG 9616 (1.2 mg/kg) IV in Cats with and without Renal Pedicle Ligation

Drug	Renal Pedicle	N	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_1 (ml/kg)	Vd_{ss} (ml/kg)	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	MRT (min)
ORG 9426	Intact	5	2.9 ± 1.4	33.1 ± 4.8	184 ± 64	579 ± 29	31.9 ± 2.6*	18.3 ± 2.1
ORG 9426	Ligated	7	2.9 ± 1.7	34.2 ± 4.3	122 ± 60	422 ± 232	20.2 ± 8.2	20.4 ± 5.1
ORG 9616	Intact	7	2.5 ± 1.5	25.9 ± 13.8*	149 ± 158	346 ± 328	28.2 ± 11.8	11.1 ± 5.9*
ORG 9616	Ligated	7	3.0 ± 1.5	49.6 ± 24.0	135 ± 76	475 ± 311	23.2 ± 3.7	19.8 ± 12.2

Mean ± SD.
$t_{1/2\alpha}$ = distribution half-life.
$t_{1/2\beta}$ = elimination half-life.
V_1 = initial volume of distribution.
Vd_{ss} = volume of distribution at steady-state.
Cl = clearance.
MRT = mean residence time.
* Significantly different from cats with renal pedicle ligation.

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TABLE 4. Cumulative Urinary and Biliary Excretion and Liver Content of ORG 9426 in Cats with and without Renal Pedicles Ligated

	Without Renal Pedicle Ligation			With Renal Pedicle Ligation	
Time (min)*	Urine	Bile	Liver	Bile	Liver
0–60	1.9 ± 4.3	41.7 ± 8.4	—	40.2 ± 10.6	—
61–120	5.8 ± 5.1	50.3 ± 8.6	—	47.7 ± 10.8	—
121–180	7.1 ± 5.7	52.2 ± 8.9	—	49.9 ± 10.9	—
181–240	7.4 ± 5.9	53.4 ± 8.9	—	51.0 ± 11.0	—
241–300	8.4 ± 5.6	54.0 ± 9.0	—	51.7 ± 11.1	—
301–360	8.7 ± 5.7	54.4 ± 9.2	21.3 ± 6.5	52.4 ± 9.2	33.5 ± 15.6

Mean percent of injected dose ± SD.

* Time after the iv bolus administration of ORG 9426, 1.5 mg/kg.

Discussion

The time course profile of ORG 9426, and to a lesser extent also that of ORG 9616, can be explained by their pharmacokinetic disposition observed in this study. In the case of ORG 9426, hepatic uptake and biliary excretion are dominant mechanisms for its clearance from plasma. These mechanisms of excretion appear to be even more dominant for ORG 9426 than for that of vecuronium. After vecuronium the biliary excretion and hepatic recovery of the parent compound is 53% of the injected dose,[7] which is markedly less than the hepatobiliary clearance of ORG 9426, which counts for 75% and 86% of the injected dose (table 4) in animals without and with renal pedicle ligation, respectively. Since only 8.7% of an injected dose appears in the urine as unchanged ORG 9426, this compound appears to be less dependent than vecuronium on the renal function for its elimination. Accordingly, the duration of action of ORG 9426 is not influenced by ligation of the renal pedicles; however, the slower clearance (tables 1 and 3) observed in this group of animals together with the observation of prolonged duration of action during hepatic exclusion (table 2) suggests that hepatic disorders alone or associated with impaired renal function may prolong the duration of action of ORG 9426. All of the ORG 9426 recovered from the biological material appeared in unchanged form only, indicating little or no biotransformation. Approximately 20% of the administered dose of ORG 9426 remained unaccounted for by hepatobiliary or urinary excretion. However, if additional tissue uptake or other pathways of elimination occur at other sites, this could only account for a negligible fraction of the total dose of this compound.

The time course of action of the 6× ED_{90} dose of ORG 9616 (tables 1 and 2) closely resembles that of succinylcholine in humans. Muir *et al.*[3] came to the same conclusion based on studies in pigs and cats. However, the ORG 9616 pharmacokinetic profile does not provide a straightforward explanation for the brevity of its neuromuscular blocking effects. More importantly, the only significant alteration in the time course of action of ORG 9616 after ligation of the renal pedicles was a paradoxical decrease of the recovery index (table 1). This is difficult to reconcile with the significant prolongation of the elimination half-life and increase of the mean residence time in the same groups of animals. Renal elimination and hepatic storage appear to be important factors in terminating the neuromuscular blocking effects of ORG 9616. The biliary excretion of the parent compound together with its 3-desacetyl metabolite, although substantial, did not account for more than 37% and 47% of the injected dose in animals without and with renal pedicle ligation, re-

TABLE 5. Cumulative Urinary Excretion of ORG 9616 and Its 3-Desacetyl Metabolite (3-OH)

Time after Injection (min)	ORG 9616	3-OH
0–60	1.4 ± 2.2	0.1 ± 0.2
60–120	2.8 ± 2.5	0.7 ± 1.1
120–180	3.9 ± 3.5	0.9 ± 1.2
180–240	4.1 ± 3.5	1.1 ± 1.3
240–300	4.3 ± 3.6	1.1 ± 1.4
300–360	4.4 ± 3.6	1.3 ± 1.4
360–420	4.5 ± 3.6	1.4 ± 1.5
420–480	4.6 ± 3.6	1.4 ± 1.5

Mean percent of injected dose ± SD.

TABLE 6. Cumulative Biliary Excretion of ORG 9616 and its 3-Desacetyl Metabolite (3-OH) in Cats with and without Renal Pedicle Ligation

	Normal		Ligated Renal Pedicles	
Time after injection	ORG 9616*	3-OH*	ORG 9616†	3-OH†
0–60	12.7 ± 12.8	4.7 ± 3.8	21.6 ± 8.3	9.9 ± 5.0
60–120	16.3 ± 13.3	8.3 ± 4.8	24.8 ± 8.9	14.0 ± 7.8
120–180	18.6 ± 13.9	11.9 ± 7.1	25.9 ± 9.2	16.1 ± 9.1
180–240	18.8 ± 14.6	12.8 ± 7.2	26.6 ± 9.5	17.5 ± 9.5
240–300	20.1 ± 14.6	14.6 ± 10.1	27.1 ± 9.7	18.3 ± 9.7
300–360	20.2 ± 14.7	15.0 ± 10.5	27.2 ± 9.7	19.0 ± 9.9
360–420	20.3 ± 14.8	15.2 ± 10.6	27.7 ± 9.8	19.1 ± 9.9
420–480	20.4 ± 14.7	15.3 ± 10.4	27.7 ± 9.8	19.1 ± 9.9

Mean percent of injected dose ± SD.
* Normal.
† Renal pedicles ligated.

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TABLE 7. Amount of ORG 9616 and Its 3-Desacetyl Metabolite in the Liver in Cats with and without Renal Pedicle Ligation

Cat	ORG 9616	3-Desacetyl Metabolite
Normal	4.2 ± 1.6	9.8 ± 4.2
Renal pedicle ligation	3.6 ± 1.3	14.5 ± 8.7

Mean percent of injected dose ± SD.

spectively. These values are in the same order of magnitude as those observed after ORG 9426 under corresponding experimental conditions (table 4). Since none of the time course variables were prolonged by either renal pedicle ligation (table 1) or by hepatic exclusion (table 2), we assume that rapid biotransformation and distribution to other unidentified tissues may occur shortly after iv administration of this drug. Consequently the duration of neuromuscular effects of ORG 9616 might be governed predominantly by the distribution half-life. This would explain the lack of effect of the altered pharmacokinetic variables on the time course profile of ORG 9616 in animals with ligated renal pedicles. Obviously the 40% of the injected dose of ORG 9616 for which we could not account for by hepatorenal excretion must be identified in further studies in order to adequately explain the time course of the pharmacologic effect of this drug.

While the main purpose of this study was to define pharmacokinetics, we believe some limited conclusions can be made regarding the time course of action of ORG 9426 and ORG 9616. The results of this study demonstrate a highly favorable difference in the time-course profile of both ORG 9426 and ORG 9616 when compared with vecuronium in the cat. The onset time, duration of action, and recovery index observed after the ED_{90} of ORG 9426 and ORG 9616 (table 2, first administration) were 1–1.2 min, 6.8–4 min, and 1.6–0.9 min, respectively, which favorably compares to the corresponding values of 4.8, 14, and 5.3 min reported for vecuronium in a similar study.[8]

It is difficult to predict what the action of these drugs will be in humans. However, we believe our data support the concept that both these drugs may offer advantages over succinylcholine in humans. These observations warrant clinical trials with both drugs with the hope that their onset time would approach that of succinylcholine.

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